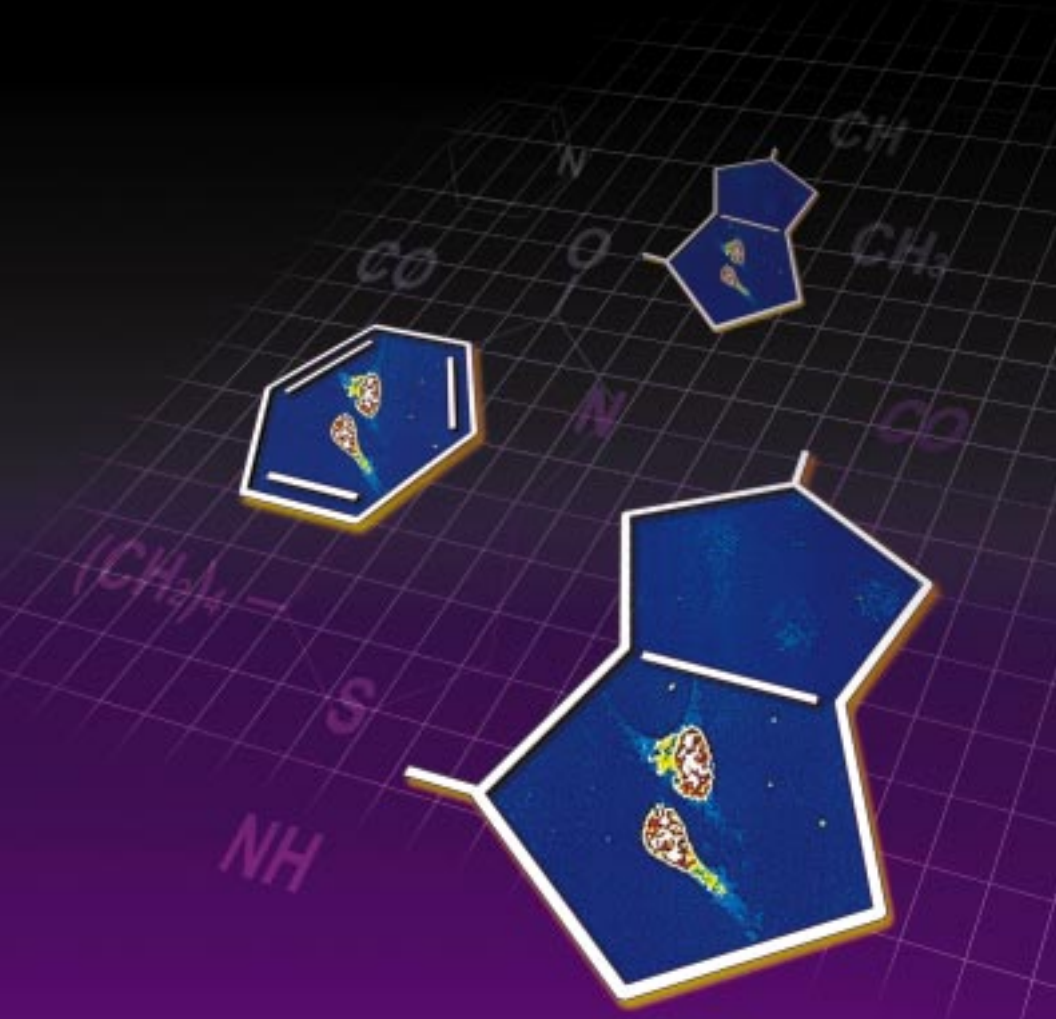
Transfection Penetratin 1™ Reagents



Novel Tool for Gene Targeting

The gene delivery company

QUANTUM

APPLICATION MANUAL

Version 1

Transfection Penetratin 1™ Reagents

APPLICATION MANUAL
Version 1

Storage Conditions

It is recommended to use microfuge tubes for storage and handling of all solutions of Penetratin 1 or Penetratin 1 conjugates. Siliconized tubes are recommended to avoid adsorption of the products onto the surface of the tubes.

Product	Storage Temperature
Lyophilized Activated Penetratin 1:	-20ºC
Lyophilized Biotinylated Activated Penetratin 1:	-20ºC
Aqueous solutions of Activated Penetratin 1, or Biotinylated Penetratin 1:	-80ºC
Penetratin 1, or Biotinylated Penetratin 1 coupled with oligonucleotides or peptides (aqueous solutions)	-80ºC

Very important: Solutions must be aliquoted. Avoid freezing/thawing cycles.

For research use only

We sell our products for research purpose only. They shall not be used as food, drugs, medical diagnostics or for any common uses and shall not enter the manufacturing of any of the above. Our customers are solely responsible for the hazards of using our products especially concerning their potential toxicity or pathogenicity. Some of our products are hazardous and most of our products have not been tested for their toxicity or carcenogenicity. The absence of warning label on a product does not preclude a possible health hazard. When using our products due care should be exercised to prevent human contact or ingestion. Trained personnel should handle all preparation. The Customer holds harmless both Quantum Biotechnologies and Quantum Biotechnologies' suppliers of any judicial pursuit of a third party against the above. The Customer is solely responsible for compliance with any law and regulation applying in the area.

The patented peptide Penetratin 1 has been demonstrated to exhibit unexpected properties when added to cell culture or injected *in vivo*. This 16 amino acids peptide is very efficiently captured by cells and conveyed to their cytoplasm and nuclei. This phenomenon, which is energy-independent, allows the Penetratin 1 peptide to be used as a new internalization vector. This new tool for molecular biologists has many potential applications for research and therapeutic developments.

The Penetratin 1 peptide has been discovered during research carried out by a team of French scientists (Alain Prochiantz, CNRS, URA 1414, École Normale Supérieure, Paris) on the DNA-binding region of the *Drosophila antennapedia* homeoprotein.

They demonstrated that the 60 amino acid-long homeobox of *Drosophila antennapedia* (pAntp) was able to cross the plasma membrane in culture and to accumulate in the cytoplasm and nucleus. They immediately investigated whether chimeric molecules would behave in a similar manner. They demonstrated that such a chimeric molecule crosses the membrane of myoblasts, myotubes, neurons and numerous other cell types, and is conveyed to their nuclei and cytoplasm.

The sequence involved in the uptake process has been determined. This 16 amino acid-sequence called Penetratin 1 peptide, is exclusively available from Quantum Biotechnologies for research use. This revolutionary tool for modern molecular biology is patented worldwide [licence CNRS, École Normale Supérieure (ENS), Laboratoire de Développement et Évolution du Système Nerveux, URA CNRS 1414].

2.1 Non-Traumatical Internalization

The use of the new Penetratin 1 peptide provides a non-traumatic protocol for the introduction of molecules into a large number of living cells.

Introducing foreign molecules into living eukaryotic cells is commonly achieved either by transfection of expression vectors or by injection and scrape loading protocols (such as trituration). These approaches, although very useful, suffer severe limitations, in particular in the yield of modified cells and the disruption of the cell membranes.

A less invasive way to introduce molecules into cells is to link them to other molecules normally internalized (such as folate or bacterial toxins). Nevertheless, such systems are dependent upon classical endocytosis and are therefore limited by endosomal degradation. Therefore, the development of molecules such as the Penetratin 1 peptide, able to serve as transmembrane carriers in order to introduce macromolecules into the cytoplasm or the nucleus of large numbers of living cells, is of great interest.

2.2 Low Concentrations Required for Internalization

Cells are incubated for 2.5 hours with concentrations ranging from 50 nM to 400 nM of Penetratin 1 peptide. No cytotoxic effect has been reported up to 36 µM.

2.3 Right to the Cell

All data strongly suggest that the Penetratin 1 peptide is not targeted to the lysosomal compartment. Successful internalization has been carried out at low temperature (+ 4ºC), suggesting an energy-independent mechanism of translocation involving classical endocytosis. This provides a distinct advantage when it comes to internalising molecules without endosomal degradation.

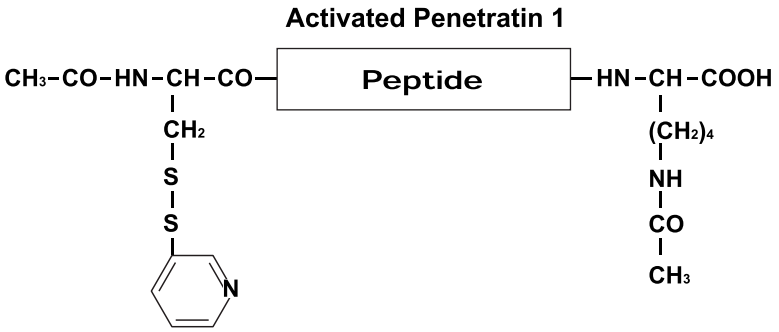
Other polypeptides that cross biological membranes are those destined, after synthesis, to specific intracellular compartments such as the endoplasmic reticulum or the mitochondria. Passage through these intracellular membranes requires the presence of specific proteins that serve as receptor, and/or channel. Many results suggest that uptake of the Penetratin 1 peptide does not involve such a specific mechanism. It has been demonstrated that the transport mechanism involved in the uptake of the pAntp sequence cannot be saturated. This finding and the internalization at + 4ºC suggest that the polypeptides do not bind a transporter.

2.4 A Universal Vector

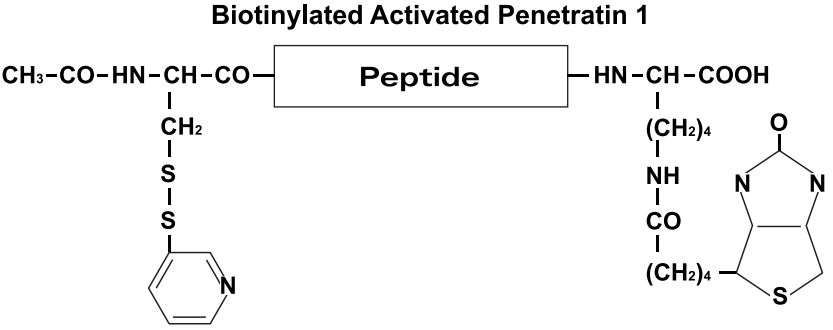
Although the internalization mechanism is not yet fully understood, such an energy-independent mechanism, which cannot be saturated, is expected to be poorly specific. Indeed, the entire homeodomain is internalized by all cell types tested (although it is preferentially captured by cells expressing high levels of polysialic acids on their surface). Myoblasts, myotubes, neurons, astrocytes, fibroblasts, lymphocytes, oligodendrocytes, macrophages, pituitary cells and several cell strains (NIH 3T3, Ltk, PC12, CHO, neuroblastoma and glioma from different origins, human HaCa T cells and human macrophages) have been successfully tested. Potential applications are antisense or antigene strategies, or drug targeting. Oligopeptides up to 100 amino acids in length have been successfully internalized using Penetratin 1 (Deschamps *et al*. 1992).

3.1 Chemical structure of Penetratin 1

3.1.1 Activated Penetratin 1 (MW: 2715.3, as determined by mass spectrometry)



3.1.2 Biotinylated Activated Penetratin 1 (MW: 2899.2, as determined by mass spectrometry)



3.2 Quality Control

Activated Penetratin and biotinylated activated Penetratin 1 are delivered HPLC purified. Quality control includes HPLC, capillary electrophoresis and mass spectrometry.

HPLC quality control:

Column: Nucleosil C18 5 µm 100A 2.1 mm x 250 mm
Flow rate: 0.3 mL/min
CH_3CN gradient from 0 to 60% within 60 minutes
Detection: 200 nm

Capillary electrophoresis:

Citrate buffer: 20 mM, pH 2.5
Voltage: 30 kV
Detection: 200 nm

4.1 Coupling Penetratin 1 onto an Oligonucleotide

Oligonucleotides should contain a thiol function at one end. The thiol function will be involved in the coupling reaction. The Activated Penetratin 1 peptide features a pyridyl disulfite function at its N-terminal end. Equimolar amounts of Penetratin 1 and oligonucleotide are first incubated for 15 min. at 65ºC in order to eliminate secondary structures and to prevent precipitation. Coupling is then carried out by incubating the mixture for at least one hour at 37ºC. Incubation can be carried out in water. After incubation, both molecules are linked together by means of a disulfide bond. Solutions of coupled Penetratin 1 -oligonucleotide should be aliquoted and kept at -80ºC. Reducing medium (e.g. dithiothreitol (DTT)) would cleave the disulfide bond.

4.1.1 Standard Protocol for Coupling Penetratin 1

This protocol has been used for coupling a 25-mers HPLC purified [ß]-oligodeoxynucleotide, synthesized by Quantum Biotechnologies, having its 5'-end derivatized by a thiol function (-SH) and lyophilized with DTT. Oligonucleotide sequence: CGA CGA TCA GGT GCC CCA CGA CTA G, M.W.: 8,458 (i.e. 35.92 mg/OD_{260}). Amount in the vial: approximately 10 OD_{260} of oligonucleotide (NB: one OD_{260} is the amount of oligonucleotide which gives an absorbance of 1 at 260 nm when resuspended in 1 mL of water).

WARNING: Make sure that water and solutions have been degassed.

1. Resuspend 10 OD_{260} (i.e. 4.25 x 10^{-8} moles) of the oligonucleotide in 250 µL of a 0.1 M DTT aqueous solution.
2. Mix by vortexing gently and incubate overnight at 37ºC.
3. Add 500 µL degassed water to the Activated Penetratin 1 to prepare a 1 mg/mL solution.
4. Mix by vortexing gently.
5. Remove DTT from the oligonucleotide solution by gel filtration using degassed water as an eluant.
6. Collect the oligonucleotide in 115 µL of the Activated Penetratin 1 solution (i.e. 4.25 x 10^{-8} moles)

NB: If precipitation is observed, add 1 or 2 mL methanol (saturated with N_2) and mix by vortexing.

7. Heat at 65ºC for 15 minutes. in a tightly sealed tube, then incubate at 37ºC for one hour.
8. If required, evaporate methanol using a centrifugal evaporator.

Using this protocol, a coupling yield of more than 98% is normally achieved as determined by gel electrophoresis.

4.1.2 Monitoring of the Coupling Reaction

Coupling is monitored by means of SDS-PAGE.

1. Prepare a SDS-PAGE as indicated:
   Acrylamide:bis-acrylamide: 37.5:1;
   Stacking gel: 6% acrylamide solution, 0.1% SDS, Tris 125 mM, pH 6.8
   Lower gel: 15% acrylamide solution, 0.1% SDS, Tris 375 mM, pH 8.8
   Running buffer: Tris 25 mM, 0.1% SDS, Glycine 200 mM, pH 8.5

2. Remove a small aliquot of coupled Penetratin 1 -oligonucleotide and add DTT to the solution up to a final concentration of 0.05 M.

3. Incubate at 37ºC for 1 hour. Load the following samples on parallel lanes (load approximately 10 to 20 µg equivalent Penetratin 1 in each slot):
   Lane 1: Coupled Penetratin 1 -oligonucleotide.
   Lane 2: Uncoupled Activated Penetratin 1.
   Lane 3: Sample of Penetratin 1 -oligonucleotide which has been reduced by means of the DTT solution.

4. Fix the gel using a methanol:water:acetic acid mixture (5:5:1 in volume). Immerse the gel for 30 minutes at room temperature. Staining is achieved using Coomassie Blue G250 at 0.1% in the fixation solution for 45 minutes.

5. Rinse using an acetic acid:ethanol:water solution (1:1:8 in volume) in order to remove the excess dye.

The coupled products (lane 1) migrate at a significantly lower rate than the Activated Penetratin 1 (lane 2). Penetratin 1 (produced by DTT reduction) migrates at the same position as the original activated Penetratin 1. Note that the pyridyl group of the Activated Penetratin 1 can be partially released during electrophoresis, therefore there can be two bands in lane 2 instead of one.

4.2 Coupling Activated Penetratin 1 onto a Peptide

The peptide which has to be tethered to the Penetratin 1 should feature a thiol function. Make sure this function has not been changed into disulfide bond during storage of the peptide. In this case, the peptide has to be reduced to thiol prior to coupling. Reduction can be made for example by resuspending the peptide in a degassed aqueous solution of TCEP [Tris (2-Carboxy Ethyl) Phosphate]. For more details, see reference: Derossi *et al.* 1996. Add an equimolar amount of the Activated Penetratin 1 (which features an S-S-Pyridyl function) to the solution and let incubate for approximately 2 hours at room temperature. The conjugated peptides can be subsequently purified by means of HPLC.

Coupling can also be monitored by SDS-PAGE using appropriate polyacrylamide percentage. For example, a SDS-PAGE with 18% acrylamide can be prepared. Staining can be carried out in the same way as for the analysis of Penetratin 1 -oligonucleotides conjugates.

These data are only rough indications. Protocols have to be optimized by the user.

- Recommended Penetratin 1 concentration in the culture medium: 50 nM to 400 nM. No noticeable cytotoxic effect has been reported up to 36 µM Penetratin 1 concentration.

- Before use in cell culture, dilute the peptide or the conjugate. For instance, prepare a 2X concentrated solution before adding it to cell culture. Do not add concentrated Penetratin 1 or Penetratin 1 conjugate solution to the cell culture. The uptake efficiency of Penetratin 1 by cells is so high that diffusion of concentrated solutions is very limited.

- Make sure to remove all remaining traces of double stranded DNA (dsDNA) that may be solubilized in the culture medium. Removal of solubilized dsDNA can be achieved either by washing the cell culture thoroughly or by means of an incubation with DNase I (for instance at 10 µg/mL). After DNase incubation, the cells have to be thoroughly washed. Traces of DNA in the cell culture would adsorb Penetratin 1, making it unavailable for cell uptake.

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7.1 Available Products

The Penetratin 1 peptide is available from Quantum Biotechnologies under different forms: reagent for research or as a custom service product.

7.1.1 Reagents for Research

Quantum Biotechnologies has prepared activated forms of the Penetratin 1:

- "Activated Penetratin 1": peptide with a S-S-Pyridyl function for easy coupling with molecules containing thiol (-SH) functions. The S-S-pyridyl is at the N-terminal end of the Penetratin 1 peptide.

- "Biotinylated activated Penetratin 1": peptide with S-S-Pyridyl function and a biotin for easy monitoring of the uptake of the molecule by means of a suitable avidin reagent. The S-S-pyridyl is at the N-terminal end of the peptide while biotin is linked to its C-terminal end.

Reagents for Research

Cat	Product	Size
151300	Activated Penetratin 1	500 µg
151301	Biotinylated Activated Penetratin 1	500 µg

7.1.2 Custom Services

"Penetratin 1 –Oligos" are available as a custom service. Quantum Biotechnologies will prepare your oligonucleotide sequence with the Penetratin 1. The peptide will be linked to the HPLC purified oligonucleotide sequence via a disulfide bond. It can be linked to either the 5'- or 3'-end of the oligonucleotide. Penetratin 1 - oligonucleotides production is completed within 2-3 weeks.

The conjugated sequence is delivered as an aqueous solution. The minimal amount guaranteed is 10 OD_{260}. Penetratin 1 peptide derivatized oligonucleotide sequences can be prepared from phosphodiester as well as from phosphorothioate oligonucleotides.

Other modifications compatible with the presence of the Penetratin 1 peptide on the 3'-end of the oligonucleotide are Acridine, Psoralen, -NH_2, Biotin, Fluorescein, Phosphate, Tetramethyl Rhodamine, Texas Red. Modifications compatible with the peptide linked on the 5'-end of the oligonucleotide are Acridine, Psoralene, -NH_2, Biotin, Fluorescein and Phosphate.

Please inquire for pricing.

Custom Services

Services	Size
5' modification with Penetratin 1	10 and 50 OD
5' modification with biotinylated Penetratin 1	10 and 50 OD
3' modification with Penetratin 1	10 and 50 OD
3' modification with biotinylated Penetratin 1	10 and 50 OD

7.2 Questions & Answers on Penetratin 1

1-How is Penetratin linked to oligonucleotides or peptides?

The Penetratin is linked to the oligonucleotide or to the peptide with a disulfide bond. The oligonucleotide must have an active thiol function at the 3' end or 5' end. For peptides, the same applies, however if there are several cytosines in the peptide, the Penetratin will bind to any of the cytosine.

2-What are the Penetratin products that we offer?

We supply either activated Penetratin or biotinylated activated Penetratin, both ready to be linked. The packaging size is 500 µg each. The customer can carry out the coupling by himself. We also offer a custom synthesis of oligonucleotides to be linked to Penetratin or biotinylated Penetratin. For many customers the latter is the best choice, since we can guarantee the coupling reaction.

3-Has Penetratin been tested with specific cells?

Internalization using Penetratin has been carried out in many cells and the results have been published. The list is available upon request.

4-What are the biggest oligonucleotides or peptides that have been internalized?

Oligonucleotides up to 55 bases and peptides below 100 amino acids have been internalized using Penetratin.

5-Is it possible for the customers to perform the coupling reaction by themselves?

Yes, certainly. We supply the exact protocol and we provide assistance. However, as we have the expertise we suggest that the customers let us perform the coupling.

6-What are the references?

We have a list of articles on Penetratin that we regularly update. Please contact us to obtain the updated list.

7-What type of labeling is available?

We sell biotinylated Penetratin. It is also possible to add a FITC label, which is coupled to the Penetratin. We are currently investigating to add more flurophores.

8-There is no internalization: why?

First, it is necessary to verify that the oligonucleotide or the peptide is linked to the Penetratin. The QC on coupling is made by running the complex on a PAGE gel. There should only be one band.

Second, verify that there is no DNA in the medium because the DNA adsorbs Penetratin. The concentration of serum in the medium is also important. The recommended concentration is 0.5 percent.

9-Is it necessary to protect the Penetratin-coupled oligonucleotide against nucleases?

Yes, if you want to use the Penetratin-coupled oligonucleotide for antisense studies. We suggest protecting the extremities of the oligonucleotide with phosphorothiate bonds between the last 3 bases. It is not necessary to protect the phosphodiester bonds between all the bases.

10-Quotations

Contact us for more information

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Fax: 33.3.88.67.19.45
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E-mail: info@quantum-appligene.com

7.3 Successfully Internalized Cargoes

Review of cargoes that have successfully been internalized using vector peptides derived from Antp-HD

(from:Prochiantz, A. Getting hydrophilic compounds into cells: lessons from homeopeptides, Current Opinion in Neurobiology 1996, 6:629-634

Oligonucleotides

Type of cargo	Lenght (*nt*)	Cell type	Reference
SOD1	21	Neuron	[1]
ßAPP	15	Neuron	[2]
ßAPP	25	Neuron	[2]
Hoxc-B	15	Neuron	[3]

Oligopeptides

Type of cargo	Lenght (*aa*)	Cell type	Reference
PKC Inhibitor	14	Neuron	[4]
PKC Inhibitor	14	Astrocytes	[4]
FGF-R1	09	Neuron	[5]
pCw3 (1)	41	Macrophage	[6]
pCw3 (2)	31	Macrophage	[6]
pCw3 (3)	31	Macrophage	[6]
pCw3 (4)	38	Macrophage	[6]
ICE	06	Neuron, PC12 cells	[7]
rab1	31	Prolactin cells	[8]
rab2	41	Prolactin cells	[8]
rab3A	33	Prolactin cells	[8]
rab3A	33	Muscle cells	[9]
rab3B	32	Prolactin cells	[8]
p16	20	HaCaT cells	[10]

In all cases, control cargoes (same oligonucleotides, scrambled oligonucleotides or peptides, and phosphorylated peptides) have been used. The internalization of different homeodomains or full-length homeoproteins is not mentioned (see text for references).

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Transfection

Penetratin 1™ Reagents

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